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Review Article

From skin infection to invasive diseases: A descriptive review of *Staphylococcus aureus*, focusing on Panton-Valentine leucocidin and methicillin-resistant strains

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Abstract

Despite advances in scientific research, *Staphylococccus aureus* remains a pyogenic and toxigenic bacterium involved in different infections, it endowed with the capacity to infect several biotopes and cause a wide range of infections ranging from skin diseases to other serious pathologies such as pneumonia, meningitis, sepsis, osteomyelitis and infectious endocarditis. Moreover, the emergence of resistant strains constitutes a serious public health problem. Thus, the development of new active compounds from natural sources such as medicinal plants is urgently needed.

To this end, the aim of our review was to describe the state of art of infections caused by *S. aureus*, its pathogenesis, treatment and to provide a synthesis about studies reporting a bio guided isolation of most promising compounds selected for their anti-staphylococcal activity.

Keywords: bio guided fractionation; natural products; resistance; *Staphylococcus aureus*

Introduction

The emergence of antibiotic resistance constitutes a serious public health problem. Predictive models have estimated that by 2050, antimicrobial resistance will be the main cause of global death with more than 10 million deaths per year, including around 5 million in Asia, 4 million in Africa, 400.000 in Europe and 300.000 in North America (O'Neill, 2014). The additional cost attributed to antibiotic resistance will increase to 1.5 billion euros (EUR-RC, 2011) in Europe, and in the United States it would be around 55 billion $ (CDC, 2013). The World Health Organization (WHO) has sounded the alarm on the consequences of antibiotic resistance, thus it has placed a global plan action that defines several objectives mainly the development of alternative treatment (OMS, 2016). However, the problem of resistance persists and in 2020 the same organization has declared reemergence of resistant microorganisms and has insisted on the development of new therapeutic molecules (OMS, 2022). *Staphylococcus aureus* is among the pathogens resistant to treatment, it is an opportunistic and cosmopolitan bacterium that colonizes the skin and mucous membranes of humans. Within this species there are toxigenic variants such as those expressing the Panton-Valentine leucocidin toxin (PVL) which aggravates the pathology and make *S. aureus* more toxicogenic (Nakaminami *et al*., 2020;

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Petraitiene *et al.*, 2020). *S. aureus* causes a major public health problem despite advances in scientific research, it endowed with the capacity to infect several biotopes and cause a wide range of infections ranging from skin diseases to other serious pathologies such as pneumonia (Grousd et al., 2019), meningitis (Aguilar *et a*l., 2010), sepsis (Bawazir and Mustafa, 2020), osteomyelitis (Weiss *et al*., 2020), and infectious endocarditis (Selton-Suty *et al*., 2012). Transmission of *S. aureus* is both community-based and nosocomial (Chow *et al*., 2020). In addition, strains of *S. aureus* have developed multidrug resistance to different families of antibiotics. Today, more than 90% of *S. aureus* strains produce a penicillinase that limits the action of beta-lactams. Moreover, methicillin, the first semi-synthetic penicillin not susceptible to penicillinases, quickly disappointed the medical world with the emergence of strains resistant to methicillin (MRSA). In 2019, WHO has developed a new indicator of antimicrobial resistance to track the frequency of sepsis caused by MRSA and the median rate reported by 25 countries was 12.11% (OMS, 2022). In fact, the treatment of MRSA is based on glycopeptides (vancomycin). However, less susceptible strains to glycopeptides have been isolated. These isolates are called VISA (vancomycin-intermediate *S. aureus*), or more generally GISA (glycopeptide-intermediate *S. aureus*). Among the newest antibiotic on the market, linezolid (Zyvox), it was introduced to the North American market in 2000. As early as 2001, cases of MRSA resistant to linezolid have been reported (Tsiodras *et al*., 2001; Rouard *et al*., 2018).

Faced with the emergence of resistance to current antibiotics, strategies are now in place to renew therapeutic biomolecules. Pharmaceutical companies have turned away from natural products to synthetic chemistry. Thus, tens of billions of dollars have been invested in research and development (R&D), however, these new methods of discovering bioactive molecules seem to have reached certain limits (Gershell and Atkins, 2003; Butler, 2004), which may explain the interest in researching new compounds from natural sources such as medicinal plants that are endowed with a secretion of different secondary metabolites (Bérubé-Gagnon, 2006).

The aim of the present review was to describe the state of art of infections caused by *S. aureus*, its pathogenesis, treatment and to provide a synthesis about studies reporting a bioguided isolation of most promising compounds selected for their antistaphylococcal activity.

Staphylococcus aureus

The essential reservoir for *S. aureus* is humans where it lives mainly in the commensal state in moist skin areas (perineum, armpits), mucous membranes and nasal cavities (Freeman-Cook and Cook, 2006). However, these bacteria can become formidable pathogens, after an alteration of the normal skin architecture, an invasive infection could be induced (Archer, 1998). The mode of transmission of *Staphylococcus* spp. is broader. In other words, there is not a definite cycle of transmission. Air, dust, bedding, blankets, medical equipment, food, and hands are all disseminators of *S. aureus* emphasizing intra- and human-to-human transmission (Robinson et al., 2019). It is now accepted that *S. aureus* is one of the most dangerous bacteria transmitted by both community and nosocomial ways, leading to the spread of many serious infections difficult to treat.

Clinical manifestations

Infections caused by *S. aureus* can range from skin infections, which are easy to treat, to other invasive pathologies, which are much more difficult to treat or even fatal. *S. aureus* can infect the skin, respiratory, digestive, urinary and reproductive tracts and can cause serious infections of the heart and bones (Figure 1).

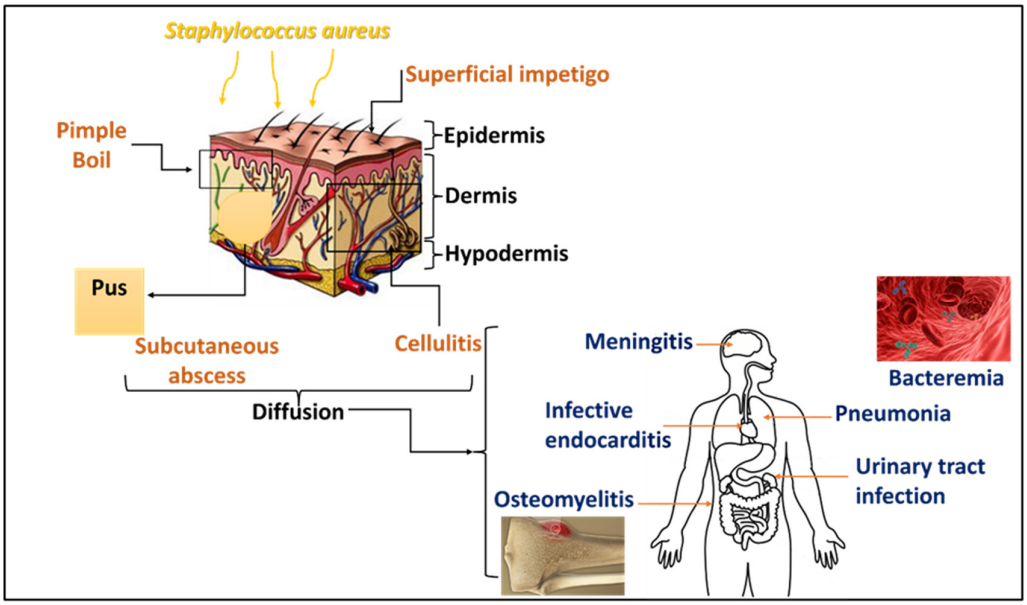

Figure 1. Skin colonization by *Staphylococcus aureus* and the resulting infections (By Zeouk, 2022)

Skin infections

According to Moran *et al.* (2006), *S. aureus* is responsible of 76% of skin and soft tissue infections (Moran *et al*., 2006b). The main skin infections caused by *S. aureus* include among others impetigo, folliculitis, boil, and skin abscess (Figure 2).

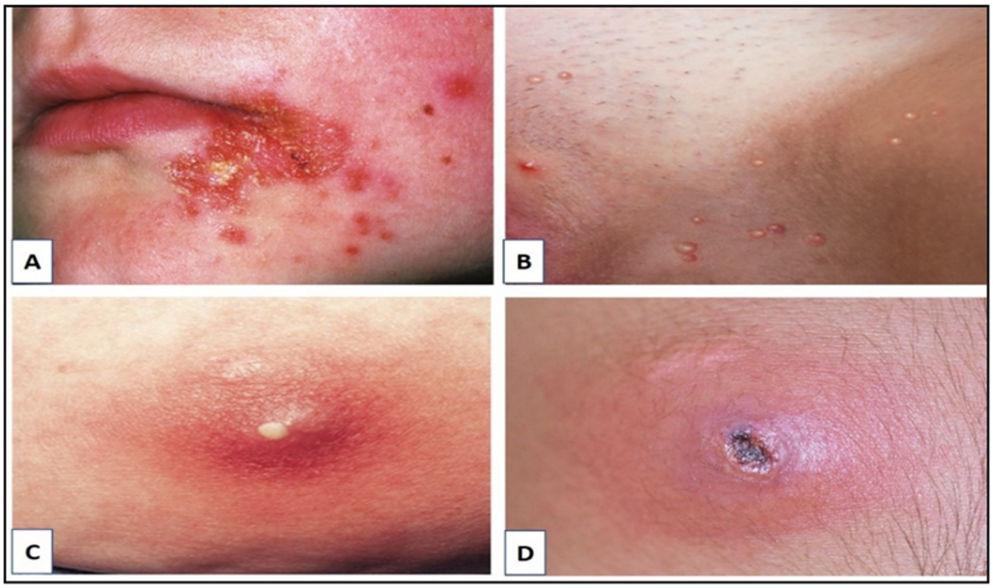

Figure 2. Common skin infections caused by *S. aureus:* A, Impetigo ; B, Folliculitis (Selk and Wood, 2019); C, Boil; D, Skin abscess

The clinical profile of these infections is different; Impetigo is manifested as pustules, vesicles, or delicate bubbles at the superficial level, most often around the mouth or nose, on the chin or behind the ears. It can also affect the trunk, buttocks, or hands. These lesions quickly become inflamed and form honey-colored scabs (Figure 2, A). It is a contagious infection that affects mainly children, but also adults with immune deficiency (Lawrence and Nopper, 2012). Folliculitis begins as small papules, with a pustule centered by a hair associated with perifollicular erythema (Figure 2, B). All parts of the body can be affected, such as the thighs, perineum, arms, back, and eyelid (Selk and Wood, 2019). The deep and necrotizing form of folliculitis with involvement of the pilosebaceous follicle in its entirety, is called a boil (Figure 2, C) which is manifested as a painful inflammatory papule or nodule centered around a pustule (Del Giudice, 2020). The boil looks similar to a skin abscess (Figure 2, D) which is also presented as a nodule or an erythematous mass, sometimes with a central pustule and spontaneous drainage of pus, but which does not have a privileged location (Kobayashi *et al*., 2015). Thus, Del Giudice (2020) has insisted on considering skin infections caused by *S. aureus* as a complex group of diseases with a very varied clinical spectrum. Moreover, skin abscesses are the most common and dangerous manifestation of *S. aureus*, because when they are pyogenic, they can develop in deeper tissues like the underlying muscles, then bacteria can spread to form abscesses throughout the internal organ system (Kobayashi *et al*., 2015). In a recent retrospective study, Rochet *et al*. (2020) have shown that the rate of patients visits for skin abscesses in the emergency department has increased significantly and that *S. aureus* was the pathogen involved in 73% of these infections (Rochet *et al*., 2020). Moreover, Ismail *et al*. (2020) have described a large epidemic of skin abscesses among gold mine employers in South Africa. *S. aureus* PVL was responsible for this epidemic, due to cross-contamination resulting from poor hygiene practices.

Invasive infections caused by *S. aureus*

S. aureus is responsible for pneumonia which can have a serious prognosis, especially those corresponding to a nosocomial infection (nosocomial pneumonia) (Grousd *et al*., 2019). In a recent study in healthcare workers, colonization of saliva by *S. aureus* was the main cause of pneumonia and the oral environment acts as a potential reservoir for lower respiratory tract infection and development of pneumonia (Chiang *et al*., 2020). Another pathology caused by *S. aureus* is meningitis, a retrospective study has shown that when caused by *S. aureus*, meningitis has devastating clinical consequences and high mortality rates (36%) due to limited treatment options (Aguilar *et al*., 2010). Other more serious diseases are osteomyelitis and endocarditis. It was reported that during osteomyelitis, *S. aureus* presented 60.5% of positive cases in culture (Weiss *et al*., 2020). In addition, another study has confirmed the high prevalence of staphylococcal osteomyelitis with 85.1% of cases (Silago *et al*., 2020). According to Urish and Cassat (2020), treatment of osteomyelitis has remained largely unchanged over the past decades and focuses on personalized antibiotic therapy with correction of medical co-morbidities (Urish and Cassat, 2020). Thus, the majority of cases of osteomyelitis have been associated with large, deep purulent collections requiring surgical debridement (Kok et al., 2018), which increasingly complicates the patients care. Furthermore, *S. aureus* is the main causative agent of infectious endocarditis associated with high death rates and embolic events (Selton-Suty *et al*., 2012). This infection has been noted to be fatal in 20% to 65% of cases, and surviving patients suffer permanent sequelae from local invasion of cardiac structures (Murray, 2005).

In addition to organic damage, the ubiquitous nature of *S. aureus* increases the risk of its passage into the blood from different primary foci by causing sepsis with distinct origins, namely cutaneous, urinary, dental and others. Indeed, MRSA sepsis was first reported as the underlying etiology of acute esophageal necrosis (Bawazir and Mustafa, 2020). In all described pathologies in the present work, one infection could be the complication of the other which is a pathological behavior frequently observed in *S. aureus*. In this sense, Al-bayati *et al*. (2020) have reported that *S. aureus* skin and soft tissue infections cause an unusual complication

of persistent bacteremia which itself leads to complicated endocarditis in addition to an affinity of the involved strain for vertebral osteomyelitis (Al-bayati *et al.*, 2020). Several studies have documented the risk of endocarditis as a complication of bacteremia and have confirmed that it is a serious complication (Bouchiat *et al*., 2015; Andersen *et al*., 2020). Furthermore, Grillo *et al*. (2020) have shown that the bacteremia itself can develop from urinary tract infections due to probing and catheterization, which leads to significant mortality considering that in many cases, the strains of MRSA were the most identified. Therefore, it is necessary to ensure the complete eradication of *S. aureus* infections and especially those of the skin.

Indeed, the ability of all these infections to be life-threatening or not depends on several factors, in particular the virulent nature of the strain in question, the host's immune response and the intensity of resistance to the clinical protocol. Several studies have confirmed that the rate of infections worldwide gradually increases with increasing drug resistance and that clinical anti-infective treatment of resistant strains has become more difficult, especially with an immune response modulated by the bacterium (Guo *et al*., 2020; Scudiero *et al*., 2020).

Anti-biotherapy and emergence of resistance

Beta-lactams, aminoglycosides, and macrolides are among the main antibiotic families used in the treatment of *S. aureus* infections (Taylor, 2013). However, *S. aureus* has a remarkable ability to acquire resistance to different antibiotics with first the appearance of resistance to penicillin which has been so prevalent that the antibiotic is no longer effective, more than 90% of the strains are resistant (Lowy, 2003). This resistance has increased because, under massive and selective use of the antibiotic, certain strains of *S. aureus* express penicillinases able to hydrolyze the active beta-lactam site of the drug (Khoshnood *et al*., 2019). To this end, scientists have developed a new semi-synthetic penicillin able to resist against hydrolysis of staphylococcal beta-lactamases, methicillin (Pottinger, 2013). However, *S. aureus* has quickly developed several resistant strains (MRSA) characterized by a modified penicillin binding protein (PBP2a/c) and which loses its affinity for most antibiotics belonging to the beta-lactam family (Gajdács, 2019). This broad-spectrum resistance is mainly due to the *mecA* and *mecC* genes, located on staphylococcal chromosomal cassette mec (SCCmec) (Paterson *et al*., 2014).

Although MRSA is the major pathogen identified in nosocomial pathologies, it is the most isolated germ also during community infections. This spread lead Moran *et al*. (2006) to suggest that among all *S. aureus* infections, a main proportion is caused by MRSA (Moran *et al*., 2006b). This suggestion has been widely confirmed in most of the skin, internal and visceral infections previously described. For example, in a study of military personnel with skin and soft tissue infections, 70% of the strains were resistant to methicillin (Landrum *et al*., 2012).

Therefore, alternative anti-MRSA treatment recommendations were developed namely vancomycin which has become the mainstay of antibiotic therapy for many forms of MRSA infections (Diaz *et al*., 2017). Its activity is due to its binding to cell wall precursors, not to PBP2 (Pottinger, 2013). However, a phenomenon of gradual increase in MICs (minimum inhibitory concentrations) has been reported in many *S. aureus* isolates leading to the emergence of VISA (Vancomycin intermediate-resistant *S. aureus*), VRSA (Vancomycin - resistant *S. aureus*) and hetero-VRSA (Ahmad *et al*., 2018).

Because of the rapid emergence of resistance in *S. aureus* strains and the spread of invasive MRSA infections, other antibiotics have been used. In a recent review, Guo *et al*. (2020) have documented the anti-MRSA antibiotic therapy and have reported that daptomycin is effective in the treatment of skin infections and bacteremia caused by MRSA. Unfortunately, the use of this antibiotic is limited in pneumonia because its mechanism of action is based on the destruction of the electrical potential of the plasma membrane without inhibiting the lipoteichoic acid, thus in the respiratory system, its activity is blocked by the alveolar surfactant

(Taylor and Palmer, 2016). Moreover, Roch *et al.* (2017) have described a clinical case with MRSA infection in which the strain isolated was resistant to daptomycin (Roch *et al*., 2017). Indeed, MRSA have not developed resistance only to daptomycin but also to tetracycline and ciprofloxacin *(Lai et al*., 2017).

Recently, Yamashita *et al.* (2019) have conducted a comparative study between daptomycin, vancomycin and azithromycin using a mouse model of MRSA pneumonia. They have demonstrated that treatment with azithromycin after 24 h of infection was effective, showing significantly longer survival and a low bacterial load in the lungs. Therefore, they suggested that this antibiotic may be a potential prophylactic agent for MRSA pneumonia (Yamashita *et al*., 2019).

Despite intensified efforts to find an effective treatment, MRSA is still a major cause of mortality and morbidity around the world. In addition, the concomitant emergence of resistance is to be expected. According to Vestergaard *et al.* (2019), multidrug resistance of MRSA has considerably complicated the difficulties of scientific research (Vestergaard *et al*., 2019b).

Virulence factors

The pathogenicity of *S. aureus* depends on many virulence factors in addition to the immune defenses of the host. These factors mainly include exoproteins such as secreted toxins (exotoxins) which disrupt host cells and interfere with immune responses, and surface proteins which play various roles in pathogenesis such as adhesion, but which is not a direct cause of toxicity towards host tissues (Vincenot *et al*., 2008).

Expression of virulence factors by to *S. aureus*

The pathophysiology of *S. aureus* infections begins with the colonization of surfaces producing different kinds of adhesion molecules, adhesins. Among the most important molecules is protein A which is a key factor in infections establishment (Palmqvist *et al*., 2002). Depending on the state of the host cell, protein A can act either by disguising *S. aureus* from the host's immune system by allowing it to resist against phagocytosis, or by completely deactivating the humoral immune response, or by inducing inflammatory cytokines and chemokines (Falugi *et al*., 2013; Gonzalez et al., 2019). In addition to protein A, some strains can form a microcapsule or develop a viscous polysaccharide substance called *slime* (Baselga *et al*., 1993). After attachment to the tissues of the host cell, *S. aureus* secretes several enzymes involved in different mechanisms such as the degradation of the host tissues, which promotes the extension of the infectious focus. The main extracellular enzymes include, among others, proteases, catalases, deoxyribonucleases, lipases, phosphatases, hyaluronidases and coagulases ... For example, Lehman *et al.* (2019) have shown that during the proliferation of skin abscesses, staphylococcal proteases played an important role in the digestion of peptides and amino acids necessary for the nutrient metabolism of *S. aureus.* In addition, the overexpression of these proteases was involved in the elevated pathogenesis of *Fak* (Fatty acid kinase) during skin infection (Ridder e*t al*., 2020), while Treffon *et al.* (2020) have concluded that the two superoxide dismutases (SodA and SodM)- typical of *S. aureus*- compensates the survival of this bacterium during the destruction of leukocytes, which confirms that the interaction between these two enzymes is at the origin of the virulence and the persistence of *S. aureus* in the respiratory tracts and during cystic fibrosis, in addition to triggering inflammatory reactions and the fight against oxidative stress (Treffon *et al*., 2020).

Other enzymes allow *S. aureus* to fight oxidative reactions, such as catalase which converts hydrogen peroxide into water and oxygen (Mandell, 1975). At the same time, *S. aureus* produces around forty exotoxins that make up about 10% of the total secretome, many of which have same functions due to remarkable structural similarity. According to their functions, several studies have shown that exotoxins fall into three main groups namely cytotoxins which act on the membranes of host cells leading to cell lysis and inflammation,

toxic enzymes which damage host cells, and superantigens involved in the massive production of cytokines inducing proliferation of T and B cells (Tam and Torres, 2018). Major toxins include hemolysins, leukocidins, exfoliatins, enterotoxins, and toxic shock toxin.

The toxin known as Panton-Valentine leukocidin (PVL) is known worldwide for its potential role in virulence and for its involvement in invasive infections. Thus, although only 5% of *S. aureus* strains produce PVL, it was widely studied. Indeed, PVL only causes cytotoxic changes in human monocytes and rabbits, because the cytotoxic activity towards these cells is highly specific and targets receptors coupled to human G proteins and those of rabbits (Spaan *et al*., 2015), therefore, these models are a good approach to better understand the complexity and pathology mediated by PVL. In this context, several studies have developed animal models on rabbits and have shown that individuals infected with wild-type PVL+ strains have developed more severe infections and higher mortality rates compared to individuals infected with PVL- strains (Diep *et al*., 2010; Lipinska *et al*., 2011). Moreover, to assess the production of PVL during human infections, Nakaminami *et al*. (2020) have conducted a recent study in which they have demonstrated that PVL-producing strains are widely distributed in skin infections and that the severity of these infections in patients infected with PVL+ is greater than that in patients infected with PVL- (Nakaminami *et al*., 2020). This severe progression of infections caused by PVL- producing strains has been confirmed in the literature (Petraitiene et al., 2020). Currently, Duployez *et al*. (2020) have reported a fatal case of a young adult with Covid-19, where the complication of viral infection was related to necrotizing pneumonia caused by *S. aureus* producing PVL (Duployez *et al*., 2020).

Thus, the pathogenesis of *S. aureus* involves a multitude of virulence factors that do not occur at the same time, but their production is finely coordinated, which explains the increased pathogenicity of *S. aureus* and the variation in its clinical profile. According to Jenul and Horswill (2019), the regulation of virulent factors by *S. aureus* is subject to a complex network that integrates the host and signals derived from the environment (Jenul and Horswill, 2019). One of the most studied regulatory systems is the *agr* gene which is a "quorum sensing system" and which allows *S. aureus* to discover the density of its own population and to translate this information into a specific gene expression model in order to control the expression of its genes (Butrico and Cassat, 2020).

Interaction host- *S. aureus*

In *S. aureus* infection, the pathogen is recognized by cells in the infected tissue. Many cells can fulfill this role, macrophages, monocytes and neutrophils are major players in the control of staphylococcal infections (Accarias, 2014). Indeed, the composition of the wall of *S. aureus* itself is also involved in the recognition and initiation of the host's immune defense. Among these components, lipoproteins, lipoteichoic acid (LTA) and peptidoglycan (PGN) are the predominant (Leemans *et al*., 2003). Several studies have documented the interaction between *S. aureus* wall components and the host's immune response. The synergy between LTA and PGN leads to the production of a cascade of cytokines and chemokines allowing the recruitment of inflammatory cells in the host. Protein A with LTA can also stimulate the release of these inflammatory mediators(Gómez *et al*., 2004; Wu *et al*., 2020). Nevertheless, *S. aureus* can limit phagocytosis and to attenuate the pro-inflammatory responses of the host, which favors its persistence in the microenvironment, especially by modulating macrophages, or even inducing necroptosis in these cells by the previously described virulence factors (Patou *et al*., 2008). Therefore, *S. aureus* will be able to survive and disseminate in phagocytes (Horn *et al*., 2017).

These interactions when regulated and the secreted cytokines are adjusted to balance between pro and anti-inflammatory ones, host cells successfully phagocytose and destroy the bacteria. However, *S. aureus* like any other infectious agent can also trigger an exaggerated immune response, during infection, if for example

two cytokines are secreted in a high amount, they can participate in a fatal outcome (vom Berg *et al*., 2013). Indeed, it has been shown that PVL seems to have a major impact in the amplification of the immune responses of the host, Huang *et al*. (2020) have shown in a pneumonia model that *S. aureus* PVL- was responsible for the severity of the disease by increasing the expression of pro-inflammatory cytokines (Huang *et al*., 2020). In addition to the increased production of cytokines, PVL was able to modulate the host's immune response by decreasing the expression of TFNα (Yoong and Pier, 2012).

In addition to immune responses, the metabolic pathway plays an important role in the interactions between *S. aureus* and the host. Lopez *et al*. (2017) have found that using the *Fak* enzyme complex, *S. aureus* is able to detect specific cis-unsaturated fatty acids which are very abundant in host tissue and which *S. aureus* is unable to produce (Lopez *et al*., 2017). In the same context, Potter et al. (2020) have conducted a comprehensive analysis of the metabolic needs of *S. aureus* during osteomyelitis, and they showed that the biosynthesis of aspartate represents a key metabolic node for the survival of staphylococci during infection, this biosynthesis has been greatly favored by the host's nutrient medium (Potter *et al*., 2020). Furthermore, Delekta *et al*. (2018) have shown that during infection, human lipoprotein particles provide a viable source of exogenous fatty acids for *S. aureus* (Delekta *et al*., 2018). Another study conducted by Lehman *et al*. (2019) has shown that during abscesses, collagen abundant at the site of infection in the host can serve as a nutrient reservoir for *S. aureus* overgrowth (Lehman *et al*., 2019).

Anti-*S. aureus* plant extracts and isolated active compounds

Plant extracts are an important source for the identification of active compounds against *S. aureus* (Table 1). The chemical diversity of these compounds is quite remarkable. Chabán *et al*. (2019) have conducted a bioguided fractionation of the extract prepared from the aerial part of *Lepechinia meyenii*, a species of the Lamiaceae family, selected from an ethnobotanical study. The ethanolic extract has been shown to be the most effective with MICs ranging from 62.5 to 500 µg/mL against strains of *S. aureus* resistant and sensitive to methicillin. Chemical fractionation resulted in the identification of carnosol, rosmanol and carnosic acid as active compounds with MICs ranging from 7.8 to 62.5 µg/mL against 15 strains of MRSA and 11 strains of MSSA (Chabán et al., 2019). Zheng *et al*. (2019) were interested in the study of different parts of the *Garcinia esculenta* species belonging to the Clusiaceae family and they have identified a new xanthone, (±) garciesculenxanthone C with bacteriostatic effect against MRSA, MSSA and VISA (Zheng *et al*., 2019).

Table 1. Some effective crude extract fractionated against *S. aureus*

Plants	Familly	Extract	Phytochemical families of isolated compounds	References
Lepechinia meyenii (Walp.) (Arial part)	Lamiaceae	Ethanolic	Diterpenes phenols and polyphenols	(Chabán *et al*., 2019)
Garcinia esculenta (Leave and twigs)	Clusiaceae	Ethanolic	Xanthones, biphenyles	(Zheng *et al*., 2019)
Syzygium antisepticum (Leave)	Myrtaceae	Acetone/methanol/ water	Sesquiterpenes	(Yuan and Yuk, 2018)
Pterocarpus erinaceus (Peel and root)	Fabaceae	Methanol/ Dichloromethane	Triterpenoides and steroides	(Tittikpina *et al*., 2018)
Acacia polyacantha (Leave, peel and root)	Fabaceae	Methanolic	Sterols, triterpenes, saponines, and flavonoïds	(Ashu *et al*., 2020)

Poincianella pluviosa (Peel)	Fabaceae	Ethanolic	Polyphenols	(Guidi *et al*., 2020)
Boswellia dalzielii (Peel)	Burceraceae	Methanolic	Terpenoides and triterpenes	(Tegasne *et al*., 2020)
Moringa stenopetala (Leave)	Moringinaceae	Ethanolic	Several families	(Manilal *et al*., 2020a)
Frangula alnus (Peel)	Rhamnaceae	Ethyl acetate	Phenols, flavonoids and anthraquinones	(Đukanović *et al*., 2020)
Rhamnus alaternus (Leave)	Rhamnaceae	Ethanolic	Anthraquinones Flavonoids	(Zeouk *et al*., 2021)

Sesquiterpenes have also shown significant activity against *S. aureus*. Yuan and Yuk (2018) have characterized β-caryophyllene as the main compound in the active extract of *Syzygium antisepticum*. This sesquiterpene has induced damage to *S. aureus* membrane (Yuan and Yuk, 2018). In the same year, Tittikpina *et al*. (2018) have characterized active compounds in the extract of *Pterocarpus erinaceus* of the Fabaceae family. These compounds were identified as friedeline, 2,3 dihydroxypropyloctacosanoate, and β-sitosteryl-β-D-glucopyranoside, and they have showed interesting activity against MRSA with a MIC of 4 µg/mL (Tittikpina *et al*., 2018). Several studies have confirmed the richness of Fabaceae in species with antistaphylococcal activity (Ashu *et al*., 2020; Guidi *et al*., 2020).

Recently, the bioguided fractionation of *Boswellia dalzielii* has confirmed the effectiveness of this process in the purification of compounds active against *S. aureus*. The crude extract has exhibited moderate activity (MIC = 250 µg/mL), the fractions have exhibited good activity with MICs ranging from 7.8 to 125 µg/mL, while the purified compounds from these fractions have exhibited promising activity with a MIC value of 3.125 µg/mL (Tegasne *et al*., 2020).

Further studies have considered bioguided fractionation for the discovery of compounds able to inhibit biofilm formation by *S. aureus*. In this context, Manilal *et al*. (2020) have reported the antistaphylococcal activity of *Moringa stenopetala* selected among three other species. Its ethanolic extract has shown a bacteriostatic effect against MRSA by inhibiting its growth in the preformed matrix of the biofilm. Chemical analysis of this extract revealed 12 active compounds belonging to different chemical classes (Manilal *et al*., 2020b).

Moreover, biofilm formation by *S. aureus* has been shown to be highly influenced by *Frangula alnus* extract rich in flavonoids and anthraquinones such as catechin and emodin *(Đukanović et al*., 2020). Recently, our team has conducted a bioguided fractionation of the ethanolic extract of *Rhamnus alaternus*, the purification procedure allowed us to identify the same families anthraquinone and flavonoids, emodin being the most active compound without cytotoxicity towards murine macrophages (Zeouk *et al*., 2021).

Conclusions

S. aureus represents a causative agent of different serios diseases that constitutes an increasing health problem. Current antibiotics are not satisfactory despite the advances in science. The multiplicity of diseases caused by *S. aureus* is mainly related to the strains as well as the immune response of the infected host. Thus, the development of new antibiotics with a noticeable effect and reduced toxicity remains an urgent need especially from natural antimicrobial agents, which could constitute a promising therapeutic approach.

Authors' Contributions

The author read and approved the final manuscript.

Ethical approval (for researches involving animals or humans)

Not applicable.

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Conflict of Interests

The authors declare that there are no conflicts of interest related to this article.

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